

## Synthetic Methods

## Alkoxyallene-Based LANCA Three-Component Synthesis of 1,2-Diketones, Quinoxalines, and Unique Isoindenone Dimers and a Computational Study of the Isoindenone Dimerization

Roopender Kumar,<sup>[a][‡]</sup> Mrinal K. Bera,<sup>[a][‡‡]</sup> Reinhold Zimmer,<sup>[a]</sup> Dieter Lentz,<sup>[a]</sup> Hans-Ulrich Reissig,<sup>\*[a]</sup> and Ernst-Ulrich Würthwein<sup>\*[b]</sup>

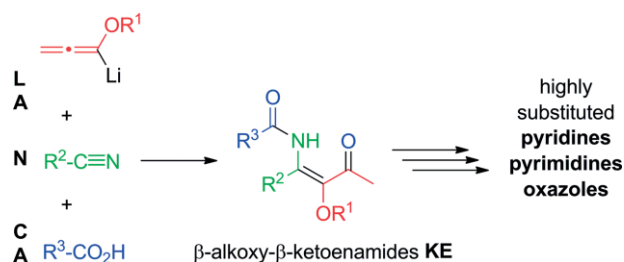
Dedicated to Professor Hiriyakkanavar Ila on the occasion of her 75th birthday

**Abstract:** A series of  $\beta$ -alkoxy- $\beta$ -ketoenamides was prepared by the well-established LANCA three-component reaction of lithiated 1-(2-trimethylsilylethoxy)-substituted allenes, nitriles, and  $\alpha,\beta$ -unsaturated carboxylic acids. The  $\alpha$ -*tert*-butyl-substituted compounds were smoothly converted into the expected 1,2-diketones by treatment with trifluoroacetic acid. A subsequent condensation of the 1,2-diketones with *o*-phenylenediamine provided the desired highly substituted quinoxalines in good overall yield. Surprisingly, the  $\alpha$ -phenyl-substituted  $\beta$ -alkoxy- $\beta$ -ketoenamides investigated afford not only the expected 1,2-diketones, but also pentacyclic compounds with an

*anti*-tricyclo[4.2.1.1<sup>2,5</sup>]deca-3,7-diene-9,10-dione core. These interesting products are very likely the result of an isoindenone dimerization which was mechanistically studied with the support of DFT calculations. Under the strongly acidic reaction conditions, a stepwise reaction is likely leading to a protonated isoindenone as reactive intermediate. It may first form a van der Waals complex with a neutral isoindenone before the two regio- and diastereoselective ring forming steps occur. Interestingly, two neutral or two protonated isoindenones are also predicted to dimerize giving the observed pentacyclic product.

## Introduction

In earlier reports we described the discovery<sup>[1]</sup> and synthetic exploration of a novel three-component reaction (LANCA reaction)<sup>[2]</sup> that employed lithiated alkoxyallenes (LA),<sup>[3]</sup> nitriles (N) and carboxylic acids (CA) and provided access to a broad range of  $\beta$ -alkoxy- $\beta$ -ketoenamides **KE** (Scheme 1). These intermediates with a unique assembly of functional groups were employed to prepare comprehensive libraries of highly substituted pyridine,<sup>[4]</sup> pyrimidine,<sup>[5]</sup> and oxazole derivatives.<sup>[6]</sup>



Scheme 1. The LANCA three-component synthesis of  $\beta$ -alkoxy- $\beta$ -ketoenamides **KE** starting from lithiated alkoxyallenes (**LA**), nitriles (**N**) and carboxylic acids (**CA**).

During our studies on the reactivity of different types of  $\beta$ -alkoxy- $\beta$ -ketoenamides **KE** we found that  $\beta$ -(2-trimethylsilylethoxy)- $\beta$ -ketoenamides **1** generally undergo a smooth acid-promoted conversion into the 5-acetyl-substituted oxazole derivatives **2** (Scheme 2). The mechanisms of the formation of  $\beta$ -alkoxy- $\beta$ -ketoenamides **KE** and their transformation into oxazoles **2** have been discussed in detail in these earlier reports.<sup>[1,6]</sup> As side-product or even as major component, simple hydrolysis of the 2-trimethylsilylethyl enol ether moiety of **1** furnished 1,2-diketones **3**. This side-reaction is generally favored when bulky substituents  $R^1$  such as *tert*-butyl or 1-adamantyl were introduced via the nitrile component into **1**.<sup>[6]</sup> In the current study, we investigate the influence of  $\alpha,\beta$ -unsaturated carboxylic acids which should incorporate an alkenyl side-

[a] Institut für Chemie und Biochemie, Freie Universität Berlin, Takustrasse 3, 14195 Berlin, Germany

E-mail: hreissig@chemie.fu-berlin.de

<http://www.bcp.fu-berlin.de/en/chemie/chemie/forschung/OrgChem/reissig/index.html>

[b] Organisch-Chemisches Institut and Center for Multiscale Theory and Computation (CMTc), Westfälische Wilhelms-Universität Münster, Corrensstrasse 40, 48149 Münster, Germany

E-mail: wurthwe@uni-muenster.de

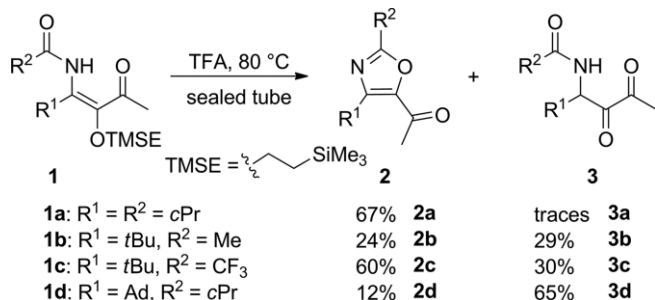
[‡] Present address: Department of Chemistry, University of Cambridge, Lensfield Road, CB2 1EW Cambridge, UK

[‡‡] Present address: Department of Chemistry, Indian Institute of Engineering Science and Technology, Shibpur, PO-Botanic Garden, Howrah-711 103 (WB), India

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under <https://doi.org/10.1002/ejoc.202000116>.

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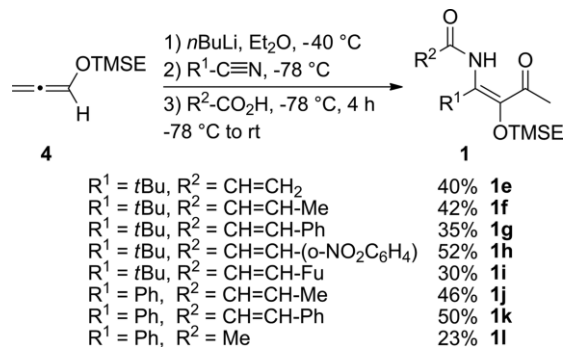
chain R<sup>2</sup> into oxazoles **2** and/or 1,2-diketones **3**. 1,2-Diketones are versatile starting materials for a variety of transformations, in particular as precursors for several classes of heterocycles.<sup>[7]</sup>



Scheme 2. Conversion of β-(2-trimethylsilyloxy)-β-ketoenamides **1** into oxazoles **2** and/or 1,2-diketones **3**.<sup>[6]</sup>

## Results and Discussion

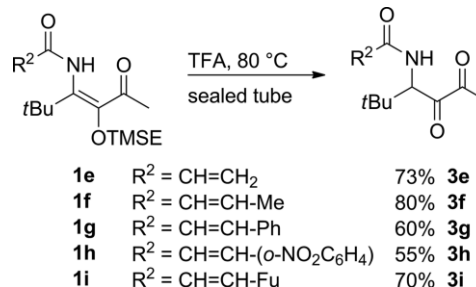
It has been demonstrated earlier that α,β-unsaturated carboxylic acids, including the sensitive acrylic acid, are well tolerated in the LANCA three-component reaction employing simple alkoxyallenes. The resulting products were smoothly transformed into pyridine and pyrimidine derivatives that now bear the corresponding alkenyl substituent introduced with the carboxylic acid.<sup>[8]</sup> When 1-(2-trimethylsilyloxy)-substituted allene **4** was treated with *n*-butyllithium and subsequently with nitriles and α,β-unsaturated carboxylic acids, we obtained the expected β-alkoxy-β-ketoenamides **1e–1k** in moderate yields, possibly diminished by formation of side-products in this step (Scheme 3). No attempts to optimize the process have been undertaken. For comparison, we also prepared *N*-acetyl-substituted compound **1l** lacking the unsaturated side chain.



Scheme 3. The LANCA three-component synthesis of β-(2-trimethylsilyloxy)-β-ketoenamides **1e–1l**.

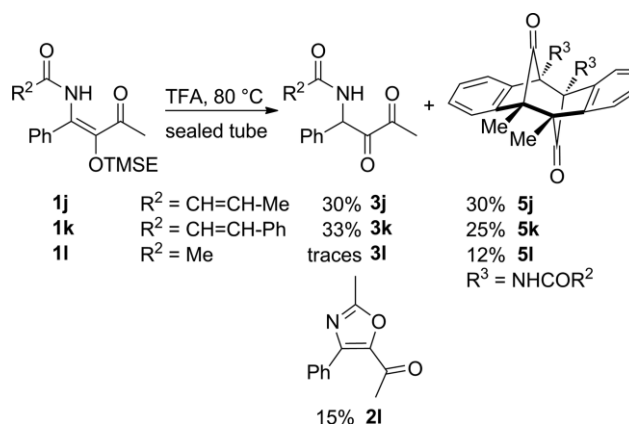
Next we examined the acid-promoted reactions of the newly prepared β-alkoxy-β-ketoenamides **1e–1l**. By treatment with trifluoroacetic acid at 80 °C the five *tert*-butyl-substituted compounds **1e–1i** gave the expected 1,2-diketones **3e–3i** in good yields (Scheme 4). The bulky substituent R<sup>1</sup> apparently suppresses cyclization to the corresponding oxazole derivatives **2**, although we cannot rigorously exclude formation of small amounts of these compounds. During oxazole formation the amide carbonyl group functions as the electrophilic unit; appar-

ently, the conjugation with the double bonds reduces the electrophilicity of the amide group. We therefore tried to enhance the reactivity by using *o*-nitrocinamic acid as precursor. However, after treatment of β-alkoxy-β-ketoenamide **1h** with trifluoroacetic acid only the 1,2-diketone **3h** was isolated in moderate yield.



Scheme 4. Trifluoroacetic acid-induced conversion of α-*tert*-butyl-substituted β-alkoxy-β-ketoenamides **1e–1i** into 1,2-diketones **3e–3i**.

With the two phenyl-substituted β-alkoxy-β-ketoenamides **1j** and **1k**, the expected 1,2-diketones **3j** and **3k** were obtained in approximately 30 % yield, whereas for the *N*-acetyl derivative **1l** only trace amounts of the corresponding 1,2-diketone **3l** were detected in the crude product mixture (Scheme 5). Instead, oxazole **2l** was isolated in 15 % yield. No oxazole derivatives were observed in the reactions of **1j** and **1k**, as opposed to the smooth conversion of β-alkoxy-β-ketoenamides with R<sup>1</sup> = R<sup>2</sup> = Ph or with R<sup>1</sup> = Ph, R<sup>2</sup> = C≡CH, where the corresponding 2,4-diphenyl-substituted or 2-ethynyl-4-phenyl-substituted oxazole derivatives were isolated in good yield.<sup>[6]</sup>



Scheme 5. Trifluoroacetic acid-induced conversion of α-phenyl-substituted β-alkoxy-β-ketoenamides **1j–1l** into 1,2-diketones **3j** and **3k** or oxazole **2l** as well as “dimeric” compounds **5j–5l**.

Surprisingly, in the three experiments a second major product was isolated in 12–30 % yield. By spectroscopy, the structure of **5j**, **5k**, and **5l** could not be determined unambiguously, although mass spectrometry indicated a “dimeric compound”, formally arising from two molecules of **3j–3l** and elimination of two molecules of water. An unequivocal structural elucidation was possible by an X-ray analysis of compound **5j** (Figure 1), showing that a compound with a C<sub>2</sub>-symmetric *anti*-tricyclo-[4.2.1.1<sup>2,5</sup>]deca-3,7-diene-9,10-dione core was formed.<sup>[9]</sup> Due to the high similarity of the NMR data of **5j** with those of

5l we can assume that the latter show the same connectivity of atoms. In the solid state, compound **5j** shows two different hydrogen bridges, one of N1–H with the carbonyl group of the

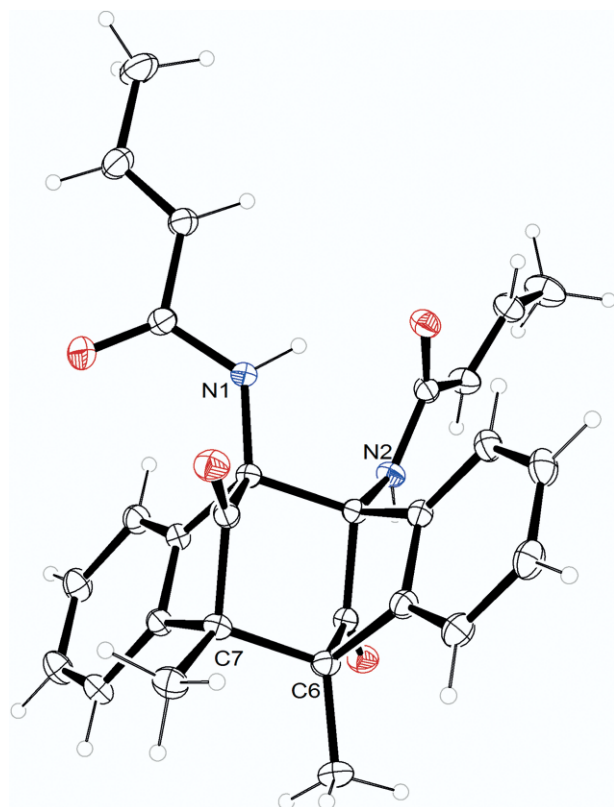
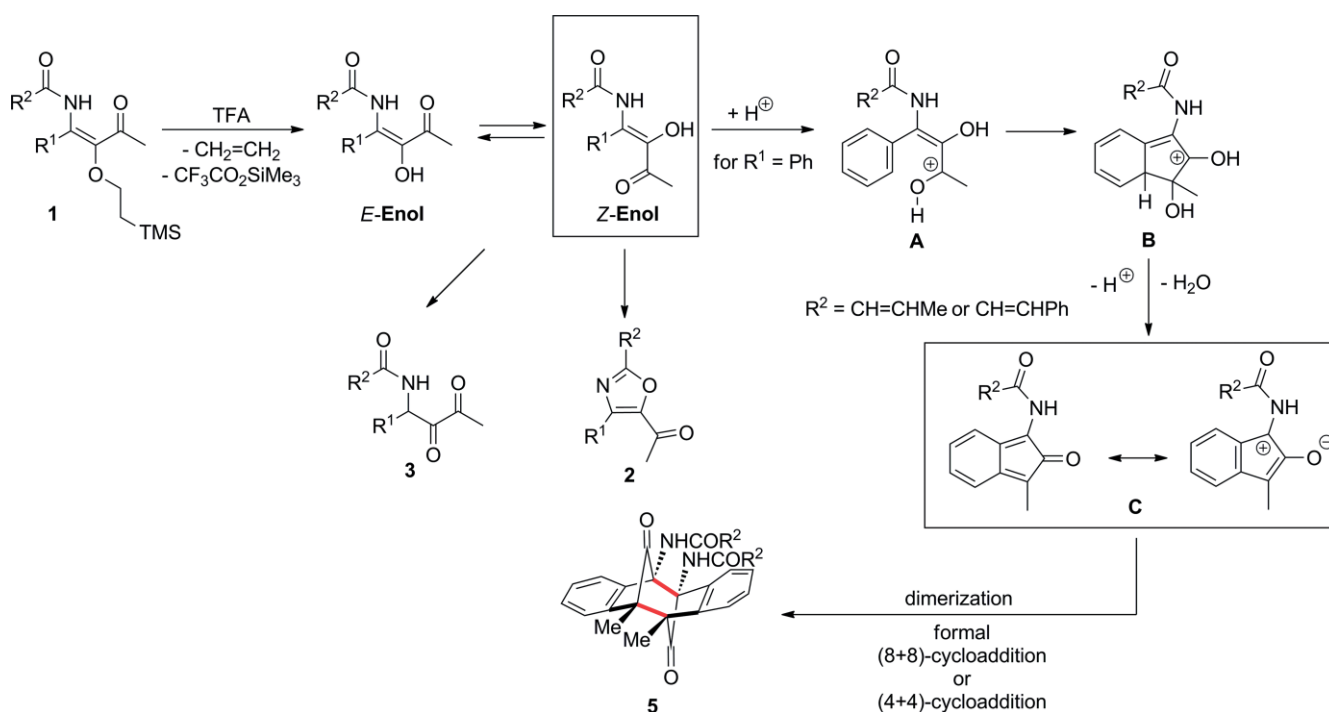


Figure 1. Solid state structure of **5j** (ORTEP plot 50 % probability level).<sup>[10]</sup>

opposite amide side chain, and the second one of N2–H to the C5 carbonyl group.

The formation of compounds **5j–5l** is apparently due to the presence of the phenyl group of **1j–1l** that underwent a cyclization reaction with the methyl-substituted carbonyl group followed by further steps. Interestingly, treatment of 1,2-diketone **3k** with trifluoroacetic acid did not lead to the “dimer” **5k**, an observation indicating that its formation does not involve the 1,2-diketone as intermediate. A speculative but plausible mechanistic scenario is depicted in Scheme 6. The deprotection of  $\beta$ -alkoxy- $\beta$ -ketoenamides **1** with acid (under desilylation and ethylene deliberation) first provides the corresponding *E*-Enol intermediates that can undergo a rapid (acid-catalyzed) *E/Z* isomerization delivering *Z*-Enols in equilibrium. Only enols with *Z*-configuration are able to undergo cyclizations involving the proximate amide carbonyl group to give oxazole derivatives **2**.<sup>[6]</sup> For intermediates with bulky groups R<sup>1</sup> the *E/Z*-equilibrium is shifted to the *E*-Enols, possibly because of steric repulsion between R<sup>1</sup> and the acetyl group. Therefore, these compounds provide mainly the 1,2-diketones **3** after a proton shift. For compounds with R<sup>1</sup> = phenyl, the *Z*-Enols can be protonated to intermediate **A** that undergoes an intramolecular electrophilic substitution at the aromatic ring to afford stabilized  $\sigma$ -complex **B**. Water elimination and deprotonation generates the 1-amido-substituted isoindenone (2-indenone) **C** as next species.

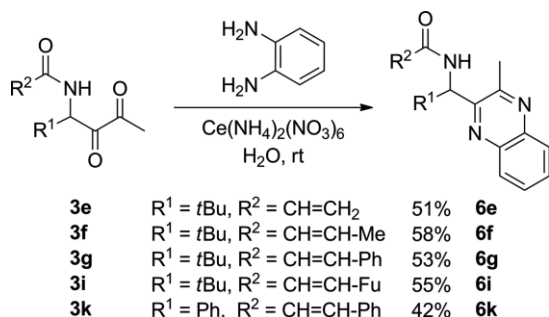
It is well known that isoindenones are highly reactive and undergo (reversible) dimerization reactions to form compounds with a central *anti*-tricyclo[4.2.1.1<sup>2,5</sup>]deca-3,7-diene-9,10-dione core.<sup>[11–13]</sup> This dimerization process can be regarded as  $[8\pi + 8\pi]$  or as  $[4\pi + 4\pi]$  cycloaddition that are formally forbidden by the Woodward-Hoffmann rules. Alternatively, it can be described as formally allowed  $[8\pi + 2\pi]$  cycloaddition if the oxy-



Scheme 6. Scenario for the formation of 1,2-diketones **3**, oxazoles **2**, isoindenones **C**, and their dimers **5**.

allyl cation moiety of the zwitterionic formula of **C** is considered. In our cases, the dimerizations leading to compounds **5** may also proceed under the influence of the strong acid trifluoroacetic acid. A detailed discussion of this process will follow under consideration of the DFT calculations (see below).

We have already demonstrated that 1,2-diketones with general structure **3** and *o*-phenylenediamine smoothly form quinoxalines **6**.<sup>[6b]</sup> We employed cerium(IV) ammonium nitrate in water as promoter of this reaction<sup>[14]</sup> which also provided the five new quinoxalines **6e–6g**, **6i**, and **6k** in 42–58 % yield (Scheme 7). Alternative methods possibly delivering higher yields were not examined. These typical examples prove that  $\alpha,\beta$ -unsaturated substituents  $R^2$  are compatible with the mild reaction conditions. The double bonds of the new quinoxaline derivatives **6** should allow further diversification of these heterocycles.<sup>[15]</sup>



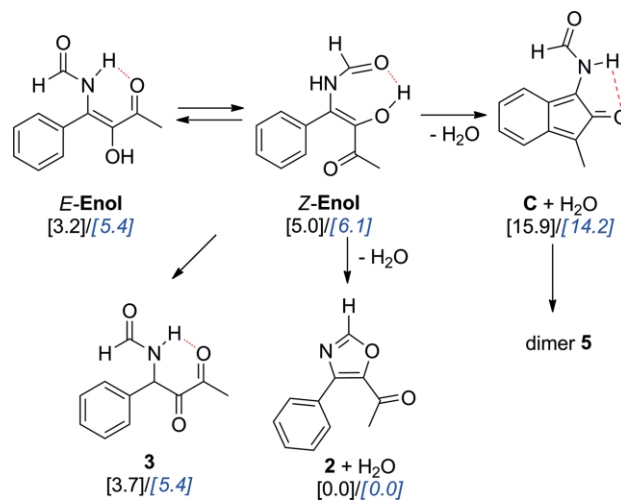
Scheme 7. Syntheses of quinoxalines **6** by condensation of 1,2-diketones **3** with *o*-phenylenediamine.

### Mechanistic Investigation by DFT Calculations

In order to investigate how realistic the reaction mechanisms shown in Scheme 6 are, quantum chemical DFT model calculations for compounds **2** and **3** with  $R^1 = Ph$  and  $R^2 = H$  (see Scheme 2) and for **5** with  $R^3 = NHCHO$  (see Scheme 5) were performed.<sup>[16]</sup> On the basis of B3LYP/6-31G(d)<sup>[17]</sup> + GD3BJ<sup>[18]</sup> geometry optimizations TPSSPTSS/def2tzvp<sup>[19]</sup> + GD3BJ optimizations for the gas phase were performed. In accord with the reaction conditions (thermal reactions) only closed shell calculations were performed, although diradical intermediates cannot be excluded. The modeling of the highly acidic trifluoroacetic acid as reaction solvent and medium is not trivial using the PCM procedure.<sup>[20]</sup> Therefore, PCM calculations (including geometry optimizations) using a solvent sphere of water as highly polar solvent were done in order to estimate the influence of a highly polar environment on the reaction mechanism and also on the intermediates and products after aqueous workup. In the following, we discuss Gibbs free enthalpies [kcal/mol], for the PCM-water model the data are given in blue [kcal/mol] (see also Supporting Information for details).

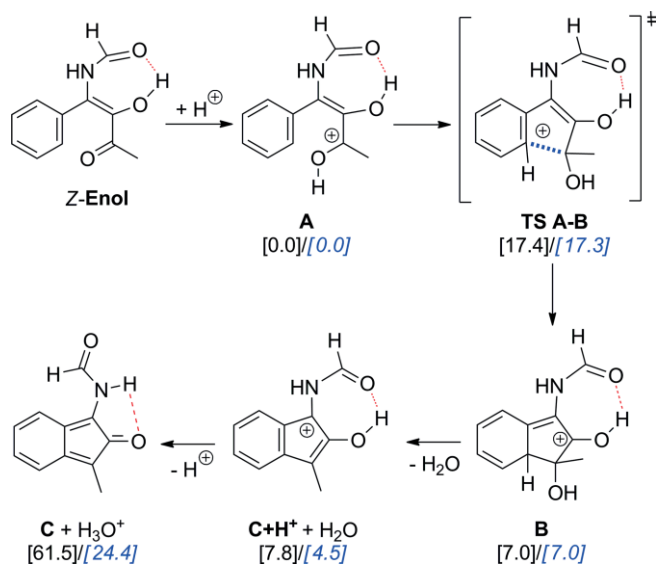
In Scheme 8 the thermodynamic properties of the neutral phenyl-substituted *E*-Enol, *Z*-Enol, 1,2-diketone **3**, oxazole **2** and isoindenone **C** are compared. Whereas the enols and the diketo form **3** as well as the oxazole derivative **2** are close in energy, interestingly the isoindenone **C** is much less stable, re-

flecting the *ortho*-chinodimethane substructure of this highly reactive intermediate (see below). The endothermicity of the later conversion indicates the necessity of proton catalysis for the next steps.



Scheme 8. Relative energies of phenyl-substituted enols, 1,2-diketone **3**, oxazole **2** and isoindenone **C** (relative Gibbs free enthalpies  $\Delta G_{298}$  are given in kcal/mol; values in blue refer to PCM-water calculations).

In Scheme 9 the energetics of the formation of isoindenone **C** from *Z*-Enol are summarized. The protonated species **A** provides via transition state **TS A-B** the  $\sigma$ -complex **B**, showing that this electrophilic substitution is slightly endergonic passing a relatively low energy barrier of 17.4 kcal/mol. The final water elimination to **C+H<sup>+</sup>** is almost energetically neutral, probably as result of compensation of the antiaromatic character of **C+H<sup>+</sup>** and the stability of the formed water molecule. Aggregation of water molecules (not considered here) certainly will make this step energetically even more favorable. For the last step (removal of the hydroxonium ion) the calculated data indicate the

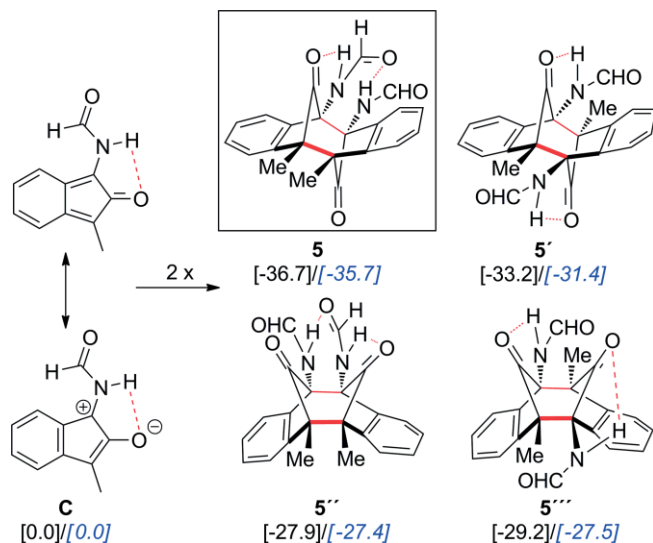


Scheme 9. Formation of **C-H<sup>+</sup>** starting from protonated species **A** via  $\sigma$ -complex **B** (relative Gibbs free enthalpies  $\Delta G_{298}$  are given in kcal/mol; values in blue refer to PCM-water calculations).



enormous basicity of compound **C** and also the solvent influence on this acid-base equilibrium.

To estimate the thermodynamics of the regio- and diastereoselective isoindenone dimerization with respect to the stability of the four possible isoindenone dimers **5–5'''** Scheme 10 shows the calculated Gibbs free reaction enthalpies. All dimers **5–5'''** incorporate two pairs of neighbored quaternary carbons.



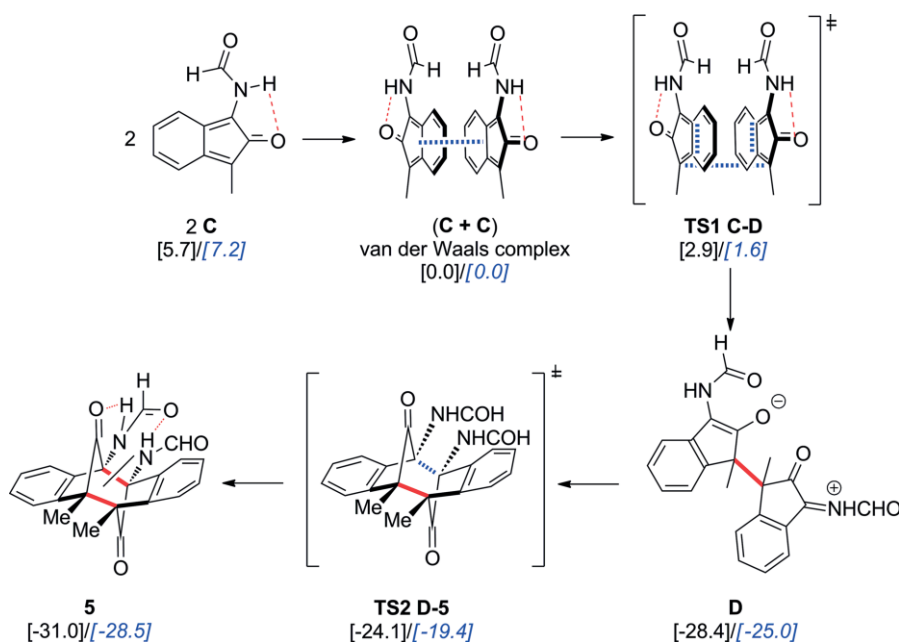
Scheme 10. Energies of dimers **5–5'''** of isoindenone **C** (relative Gibbs free enthalpies  $\Delta G_{298}$  are given in kcal/mol; values in blue refer to PCM-water calculations).

The values clearly reveal the high exothermicity of the dimerization reaction with the isolated head-to-head *anti*-dimer **5** being the most stable isomer, followed by the head-to-tail *anti*-dimer **5'** and the two *syn*-dimers **5''** and **5'''**. Besides the *syn/anti* arrangement the dimers display different possibilities

for hydrogen bonding, thus influencing the energetics of the isomers. Various possibilities were tested starting with the experimentally found structure of **5j** (X-ray), which came out to be best in energy.

In accordance with the reaction conditions (trifluoroacetic acid as reaction medium), three different scenarios were considered: dimerization of two neutral molecules **C**, reaction of **C** with **C+H<sup>+</sup>**, and finally dimerization of two protonated forms **C+H<sup>+</sup>**. A mechanistic picture of the stepwise dimerization of neutral **C** is shown in Scheme 11. At first, the exothermic formation of van der Waals complexes of two isoindenones is assumed, offering various possibilities for bond formation at the different  $\alpha$ -carbon atoms to the isoindenone carbonyl functions. Quantum chemical pathway calculations indicate a stepwise mechanism (due to the asymmetric substitution pattern of the isoindenones employed). For the experimentally observed structure **5** a C–C bond formation between the two methyl-substituted  $\alpha$ -carbon atoms turned out to be preferred. This reflects the higher reactivity of the methyl-substituted carbon atoms. The alternative approach of bond formation between the two formamide-substituted C-atoms is less favorable, most likely due to lower stabilization in the resulting intermediate. The reaction barrier **TS1 C-D** is calculated to be surprisingly low, indicating the high reactivity of the isoindenone, leading to a quite stable intermediate **D**. The next step, forming of the second C–C-bond also requires only a small barrier (**TS2 D-5**) leading to the observed product **5** with *anti* positioned carbonyl moieties as the thermodynamically most stable species within this reaction sequence. Overall, there is only a small influence of the solvent polarity on the free enthalpies.

In a similar way the reaction of one neutral molecule **C** with its protonated form **C+H<sup>+</sup>** and the dimerization of two **C+H<sup>+</sup>** molecules were investigated (Table 1, columns 3 and 4), following the same reaction sequence as studied for the dimerization



Scheme 11. Stepwise dimerization of neutral **C** via van der Waals complex (**C+C**) and transition state **TS1 C-D** to intermediate **D** followed by transition state **TS2 D-5** to isoindenone dimer **5** (relative Gibbs free enthalpies  $\Delta G_{298}$  are given in kcal/mol); values in blue refer to PCM-water calculations.

Table 1. Summary of the reactions of two neutral molecules **C**, of a neutral molecule **C** with a protonated molecule **C+H<sup>+</sup>** and of two protonated molecules **C+H<sup>+</sup>** to give the respective compounds **5**, **5+H<sup>+</sup>** and **5+2H<sup>+</sup>** (relative Gibbs free enthalpies  $\Delta G_{298}$  in kcal/mol), Column 2, 4 and 6: gas phase calculations, columns 3, 5 and 7: PCM-model for water as solvent, values in italics.

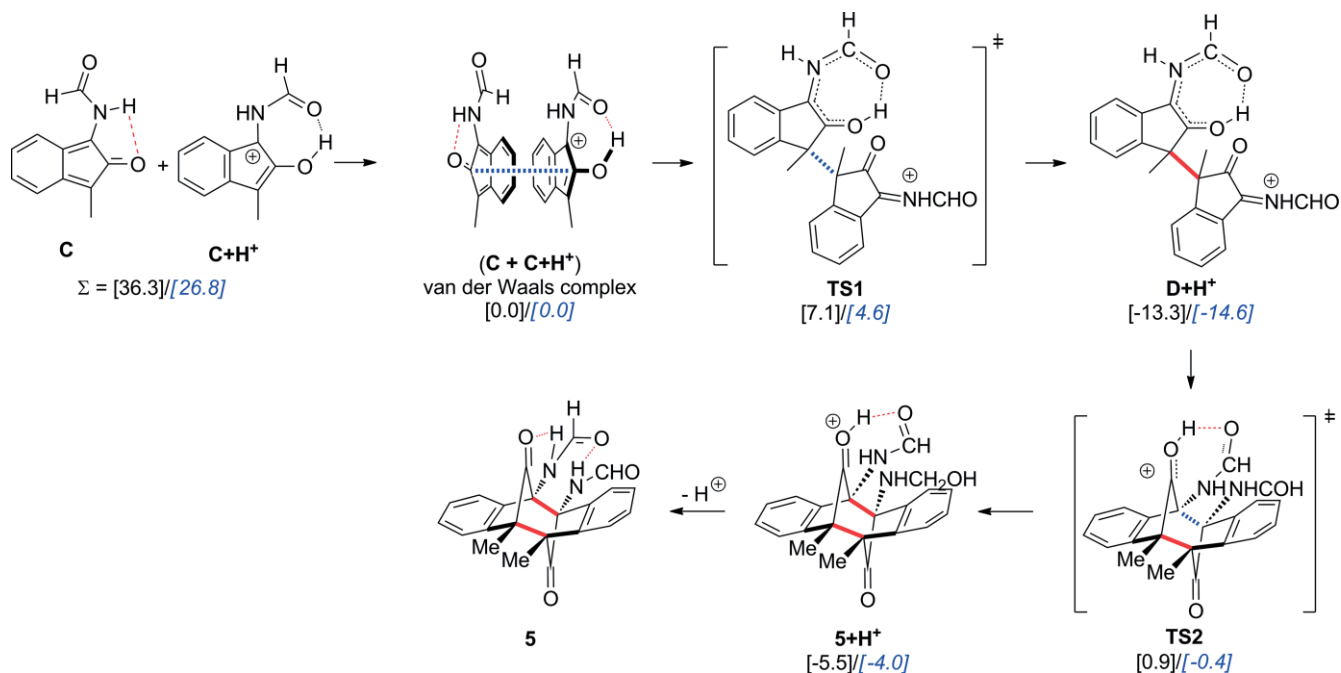
	Neutral species 2* C		Monocations C+C+H <sup>+</sup>		Dications 2* C+H <sup>+</sup>	
	$E_{rel}$ [kcal/mol] gas phase	$E_{rel}$ [kcal/mol] PCM-H <sub>2</sub> O	$E_{rel}$ [kcal/mol] gas phase	$E_{rel}$ [kcal/mol] PCM-H <sub>2</sub> O	$E_{rel}$ [kcal/mol] gas phase	$E_{rel}$ [kcal/mol] PCM-H <sub>2</sub> O
Starting material	5.7	7.2	36.3	26.8	-21.6	24.3
van der Waals complex	0.0	0.0	0.0	0.0	0.0	0.0
<b>TS1</b>	2.9	1.6	1.5	1.2	11.4	7.4
Intermediate	-28.4	-25.0	-13.3	-14.6	-5.5	-9.9
<b>TS2</b>	-24.1	-19.4	0.9	-0.4	18.1	6.8
Product	-31.0	-28.5	-5.5	-4.0	15.4	3.7

of **C**. The formation of the van der Waals complex from **C** and **C+H<sup>+</sup>** is much more exothermic, thus reflecting the favorable neutral-cation interaction (Scheme 12). Again, over a very small barrier **TS1** a quite stable intermediate **D+H<sup>+</sup>** was localized, which led to the product **5+H<sup>+</sup>** over a second relatively low transition state **TS2**. Surprisingly, product **5+H<sup>+</sup>** is higher in energy compared to **D+H<sup>+</sup>**, possibly due to the less pronounced conjugation in the product. Of course, deprotonation during the experimental procedure (aqueous workup) may form **5** by shifting the equilibrium towards this product.

For completeness, the reaction of two molecules of **C+H<sup>+</sup>** was also studied, modeling the dimerization of two protonated isoindenes in the reaction medium trifluoroacetic acid (Table 1, columns 5 and 6, for a scheme see Supporting Information). Interestingly, in spite of the two positive charges, a van der Waals complex could be localized, leading via a relatively low **TS** to a stable intermediate **D+2H<sup>+</sup>**. The later may be transformed via a reasonable **TS** into the doubly protonated product **5+2H<sup>+</sup>**, which is in the gas phase quite high in energy. Not surprisingly, the PCM-water model influences the energetics of

the reaction of these two charged species tremendously. Thus, the formation of the van der Waals complex is highly endothermic in the gas phase (repulsion of the two charges), but exothermic according to the PCM water model. The transition state **TS1** corresponds to a medium barrier and leads exothermically to the intermediate. The second barrier **TS2** is calculated to be higher than the first one (**TS1**), but still in accord with the reaction conditions applied (80 °C). The doubly protonated product is high in energy, indicating that only small amounts of it may be present in the equilibrium. Again, deprotonation of **5+2H<sup>+</sup>** may remove the neutral product **5** from the reaction mixture.

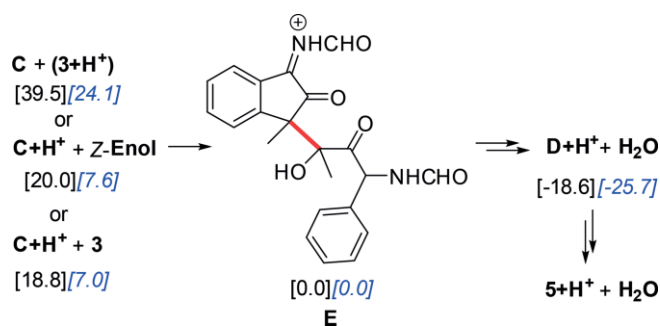
Interestingly, in all three cases stepwise reactions with relatively stable intermediates and two well defined transition states were found. Thermodynamically the formation of the first C-C bond between the methyl-substituted isoindene carbon atoms is favored over the bonding of the NHCHO-substituted isoindene carbon atoms. A synchronous (concerted)  $4\pi + 4\pi$  pericyclic reaction pathway of the asymmetric **C** could not be detected, in accordance with the Woodward-Hoffmann-rules.



Scheme 12. Stepwise reaction of **C** and **C+H<sup>+</sup>** via van der Waals complex (**C+C+H<sup>+</sup>**) and transition state **TS1** to intermediate **D+H<sup>+</sup>** followed by transition state **TS2** to protonated dimer **5+H<sup>+</sup>** (relative Gibbs free enthalpies  $\Delta G_{298}$  are given in kcal/mol; values in blue refer to PCM-water calculations).

From the thermodynamic and kinetic point of view, all three reaction pathways for the dimerization are calculated to be compatible with the reaction conditions. Thus, strong acid seems not to be a precondition for the success of the dimerization. In contrast, a basic component (e.g. **C**) or by-product or aqueous workup seem to be necessary to transfer protonated intermediates **5+H<sup>+</sup>** or **5+2H<sup>+</sup>** in the final neutral products **5**. However, it should be noted that the formation of isoindenone **C** necessarily requires acidic conditions (Scheme 9).

As alternative to the isoindenone-dimerization other mechanisms may also take place, e.g. an isoindenone unit may react with an open-chain intermediate (Scheme 13). Thus, the thermodynamics of various other reaction pathways of positively charged species were studied computationally. The reaction of **C** with protonated 1,2-diketone **3+H<sup>+</sup>** affords a positively charged intermediate **E** which is formally a water addition product of **D+H<sup>+</sup>** [-39.5 kcal/mol (gas phase), -24.1 kcal/mol (PCM-H<sub>2</sub>O)]; for details and a scheme see Supporting Information]. As second possibility to give intermediate **E**, the reaction of **C+H<sup>+</sup>** with the **Z-enol** was calculated to be less exothermic [-20.0 kcal/mol (gas phase), -7.6 kcal/mol (PCM-H<sub>2</sub>O)]. Finally, the combination of **C+H<sup>+</sup>** with 1,2-diketone **3** also may give **E** [-18.8 kcal/mol (gas phase), -7.0 kcal/mol (PCM-H<sub>2</sub>O)]. Subsequent conversions of **E** to give **D+H<sup>+</sup>** and H<sub>2</sub>O are exothermic [-18.6 kcal/mol/-25.7 kcal/mol (PCM-H<sub>2</sub>O)] allowing access to the product **5+H<sup>+</sup>** (see above, Scheme 11). In summary, all three alternative mechanisms are exothermic with respect to the starting materials. Unfortunately, all attempts to calculate the kinetics for the formation of **E** and **D+H<sup>+</sup>** were unsuccessful.



Scheme 13. Alternative pathways to give intermediate **E** and the subsequent products **D+H<sup>+</sup>** and **5+H<sup>+</sup>**.

## Conclusions

Expecting standard results for the acid-promoted hydrolysis of  $\beta$ -alkoxy- $\beta$ -ketoenamides **1** we serendipitously discovered a new route to isoindenones. Whereas  $\alpha$ -*tert*-butyl-substituted compounds **1** and trifluoroacetic acid provided the desired 1,2-diketones **3** in good yields, the  $\alpha$ -phenyl-substituted  $\beta$ -alkoxy- $\beta$ -ketoenamides afforded not only the 1,2-diketones, but also pentacyclic compounds with an *anti*-tricyclo[4.2.1.1<sup>2,5</sup>]deca-3,7-diene-9,10-dione core. This was unequivocally proven by an X-ray analysis of compound **5j**. By condensation with *o*-phenylenediamine, the 1,2-diketones **3** could be converted under mild conditions into a series of highly substituted quinoxalines **6**.

The unexpectedly isolated compounds **5** were very likely the result of a regio- and diastereoselective dimerization of intermediate isoindenones that are formed by an intramolecular electrophilic substitution process at the phenyl substituent. Comprehensive DFT calculations indicate that a stepwise dimerization process of the neutral isoindenone **C** via a van der Waals complex and a zwitterionic intermediate is energetically feasible. As alternatives, monocationic or even dicationic species were also considered. Furthermore, a synchronous  $4\pi + 4\pi$  cycloaddition – forbidden by the Woodward-Hoffmann-rules – could not be identified as possible pathway. Compounds with the rigid and functionalized pentacyclic core such as **5** could be interesting precursors for further synthetic adventures. Their simple formation from  $\beta$ -alkoxy- $\beta$ -ketoenamides **1** (or equivalent precursors) should initiate further studies.

## Experimental Section

If not stated otherwise, all reactions were carried out under argon. The solvents used were purified by distillation using common drying agents and procedures and were transferred under argon. Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded with AC 500 (Bruker), ECP 500 and ECX 400 (Jeol) spectrometers in the solvents indicated; chemical shifts ( $\delta$ ) are given in ppm relative to residual solvent peaks, coupling constants (*J*) are given in Hz. IR spectra were recorded with a Nicolet-FT-IR spectrometer or 5 SXC spectrometer, wavenumbers are given in  $\text{cm}^{-1}$ . Mass spectra were recorded with MAT 711 (EI, 80 eV, 8 kV), MAT CH7A (EI, 80 eV, 3 kV), CH5DF (FAB, 3 kV) (all Finnigan), Ionspec QFT-7 (ESI-FT ICRMS) (Varian) and Agilent 6210 (ESI-TOF, 4  $\mu\text{L}/\text{min}$ , 1.0 bar, 4 kV). Melting points: Thermovar (Reichert) melting point apparatus (not corrected). Elemental analyses: Elemental Analyzer (Perkin-Elmer), Vario EL elemental analysis system. All commercially available compounds (Acros, Lancaster, Fluka, Aldrich, TCI Europe) were used as received unless stated otherwise.

**(E)-N-[2,2-Dimethyl-5-oxo-4-[2-(trimethylsilyl)ethoxy]hex-3-en-3-yl]acrylamide (1e), Typical Procedure 1:** To a solution of TMSE-allene **4** (2.63 mL, 18.0 mmol) in dry diethyl ether (25 mL) was added *n*-butyllithium (7.18 mL, 18.0 mmol, 2.5 M in hexanes) at -50 °C. After 30 min stirring at this temperature, the mixture was cooled to -78 °C and pivalonitrile (0.50 g, 6.02 mmol) in dry diethyl ether (6 mL) was added. After stirring for 4 h at the same temperature, a solution of acrylic acid (2.16 g, 36.0 mmol) in dry diethyl ether (10 mL) was added to the reaction mixture. The temperature was allowed to rise to room temperature and the mixture was stirred overnight. The reaction was quenched with sat. aq. NaHCO<sub>3</sub> solution (30 mL) and the product was extracted with diethyl ether (3  $\times$  80 mL). The combined organic layers were washed with brine (35 mL) and finally dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, hexanes/ethyl acetate = 2:1) to obtain  $\beta$ -ketoenamide **1e** as pale yellow solid (0.75 g, 40%). M. p. 93–96 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.00 (s, 9 H, SiMe<sub>3</sub>), 1.05–1.08 (m, 2 H, SiCH<sub>2</sub>), 1.22 (s, 9 H, *t*Bu), 2.23 (s, 3 H, Me), 3.57–3.60 (m, 2 H, OCH<sub>2</sub>), 5.59 (dd, *J* = 10.5, 1.7 Hz, 1 H, =CHCO), 6.11–6.22 (m, 2 H, =CH<sub>2</sub>), 7.40 (s, 1 H, NH) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = -1.4 (q, SiMe<sub>3</sub>), 18.7 (t, CH<sub>2</sub>Si), 22.1 (q, Me), 28.5, 36.4 (q, s, *t*Bu), 69.4 (t, CH<sub>2</sub>O), 127.5, 130.5, 131.7, 150.3 (t, d, 2 s, C-2', C-3', C-1, C-2), 165.3 (s, C-1'), 201.5 (s, C-3) ppm; IR (KBr):  $\tilde{\nu}$  = 3300 (NH), 2950–2855 (=C–H, C–H), 1685–1625 (C=O, C=C)  $\text{cm}^{-1}$ ; HRMS: *m/z* [M + Na]<sup>+</sup> calcd. for C<sub>16</sub>H<sub>29</sub>NO<sub>3</sub>NaSi: 334.1809, found 334.1826; C<sub>16</sub>H<sub>29</sub>NO<sub>3</sub>Si

(311.1): calcd. C, 61.69, H, 9.38, N, 4.50; found C, 61.67; H, 9.20; N, 4.20.

**(E)-N-((E)-2,2-Dimethyl-5-oxo-4-[2-(trimethylsilyl)ethoxy]hex-3-en-3-yl)but-2-enamide (1f):** According to typical procedure 1, a mixture of TMSE-allene **4** (2.63 mL, 18.0 mmol), *n*-butyllithium (7.18 mL, 18.0 mmol, 2.5 M in hexanes), pivalonitrile (0.66 mL, 6.0 mmol) and crotonic acid (2.58 g, 30.0 mmol) in dry diethyl ether (35 mL) gave 0.823 g (42 %) of  $\beta$ -ketoenamide **1f** as a pale yellow oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.01 (s, 9 H,  $\text{SiMe}_3$ ), 1.06–1.10 (m, 2 H,  $\text{SiCH}_2$ ), 1.20 (s, 9 H, *t*Bu), 1.82 (dd,  $J$  = 6.8, 1.7 Hz, 3 H, Me), 2.24 (s, 3 H, Me), 3.60–3.63 (m, 2 H,  $\text{OCH}_2$ ), 5.83 (dq,  $J$  = 15.1, 1.7 Hz, 1 H, =CH), 6.78–6.85 (m, 1 H, =CH), 6.92 ( $s_{\text{br}}$ , 1 H, NH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –1.4 (q,  $\text{SiMe}_3$ ), 17.8 (q, C-4'), 18.8 (t,  $\text{CH}_2\text{Si}$ ), 22.2 (q, Me), 28.5, 36.4 (q, s, *t*Bu), 69.4 (t,  $\text{CH}_2\text{O}$ ), 124.7, 132.4, 141.5, 150.0 (2 d, 2 s, C-2', C-3', C-1, C-2), 165.7 (s, C-1'), 201.2 (s, C-3) ppm; IR (neat):  $\tilde{\nu}$  = 3265 (NH), 2955–2850 (=CH, C-H), 1670–1630 (C=O, C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$  calcd. for  $\text{C}_{17}\text{H}_{31}\text{NO}_3\text{NaSi}$ : 348.1971, found 348.1979.

**N-((E)-2,2-Dimethyl-5-oxo-4-[2-(trimethylsilyl)ethoxy]hex-3-en-3-yl)cinnamamide (1g):** According to typical procedure 1, a mixture of TMSE-allene **4** (2.63 mL, 18.0 mmol), *n*-butyllithium (7.18 mL, 18.0 mmol, 2.5 M in hexanes), pivalonitrile (0.50 g, 6.02 mmol) and cinnamic acid (4.98 g, 36.0 mmol) in dry diethyl ether (40 mL) gave 0.814 g (35 %) of  $\beta$ -ketoenamide **1g** as a pale yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.03 (s, 9 H,  $\text{SiMe}_3$ ), 0.96–0.98 (m, 2 H,  $\text{SiCH}_2$ ), 1.26 (s, 9 H, *t*Bu), 2.28 (s, 3 H, Me), 3.63–3.68 (m, 2 H,  $\text{OCH}_2$ ), 6.42 (d,  $J$  = 15.5 Hz, 1 H, =CH), 6.98 (s, 1 H, NH), 7.34, 7.47–7.49 (m, m, 3 H, 2 H, Ph), 7.60 (d,  $J$  = 15.5 Hz, 1 H, =CH) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –1.3 (q,  $\text{SiMe}_3$ ), 18.9 (t,  $\text{CH}_2\text{Si}$ ), 25.9 (q, C-4'), 28.7, 36.6 (q, s, *t*Bu), 69.7 (t,  $\text{CH}_2\text{O}$ ), 128.1, 128.9, 129.1, 129.9, 132.4, 134.8, 142.5, 150.1 (2 s, d, s, 4 d, C-2', C-3', C-1, C-2), 166.0 (s, C-1'), 201.4 (s, C-3) ppm; IR (neat):  $\tilde{\nu}$  = 3285 (NH), 2955–2865 (=C-H, C-H), 1690–1635 (C=O, C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$  calcd. for  $\text{C}_{22}\text{H}_{33}\text{NO}_3\text{NaSi}$ : 410.2127, found 410.2135.

**(E)-N-((E)-2,2-Dimethyl-5-oxo-4-[2-(trimethylsilyl)ethoxy]hex-3-en-3-yl)-3-(4-nitrophenyl)acrylamide (1h):** According to typical procedure 1, a mixture of TMSE-allene **4** (2.70 mL, 18.6 mmol), *n*-butyllithium (7.20 mL, 18.0 mmol, 2.5 M in hexanes), pivalonitrile (0.50 g, 6.02 mmol) and 2-nitrocinnamic acid (6.98 g, 36.0 mmol) in dry diethyl ether (35 mL) gave 1.37 g (52 %) of  $\beta$ -ketoenamide **1h** as a pale yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.00 (s, 9 H,  $\text{SiMe}_3$ ), 1.06–1.10 (m, 2 H,  $\text{SiCH}_2$ ), 1.21 (s, 9 H, *t*Bu), 2.31 (s, 3 H, Me), 3.51–3.55 (m, 2 H,  $\text{OCH}_2$ ), 6.48 (d,  $J$  = 15.5 Hz, 1 H, =CH), 7.38–7.54, 7.84–7.92 (2 m, 2 H, 3 H, Ar, =CH) ppm; IR (neat):  $\tilde{\nu}$  = 3285 (NH), 2960–2875 (=C-H, C-H), 1685–1630 (C=O, C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [ $\text{M} + \text{H}$ ] $^+$  calcd. for  $\text{C}_{22}\text{H}_{33}\text{N}_2\text{O}_5\text{Si}$ : 433.2159, found 433.2153.

**(E)-N-((E)-2,2-Dimethyl-5-oxo-4-[2-(trimethylsilyl)ethoxy]hex-3-en-3-yl)-3-(furan-2-yl)acrylamide (1i):** According to typical procedure 1, a mixture of TMSE-allene **4** (2.63 mL, 18.0 mmol), *n*-butyllithium (7.18 mL, 18.0 mmol, 2.5 M in hexanes), pivalonitrile (0.66 mL, 6.0 mmol) and 3-(2-furyl)acrylic acid (4.98 g, 36.0 mmol) in dry diethyl ether (40 mL) gave 0.680 g (30 %) of  $\beta$ -ketoenamide **1i** as a pale yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.00 (s, 9 H,  $\text{SiMe}_3$ ), 1.06–1.10 (m, 2 H,  $\text{SiCH}_2$ ), 1.20 (s, 9 H, *t*Bu), 2.27 (s, 3 H, Me), 3.59–3.64 (m, 2 H,  $\text{OCH}_2$ ), 6.32–6.35 (m, 2 H, =CH, Furyl), 6.43 (d,  $J$  = 3.3 Hz, 1 H, Furyl), 7.30 (d,  $J$  = 15.3 Hz, 1 H, =CH), 7.35 (m, 2 H, NH, Furyl);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –1.4 (q,  $\text{SiMe}_3$ ), 18.8 (t,  $\text{CH}_2\text{Si}$ ), 27.9, 28.6, 36.4 (2 q, s, Me, *t*Bu), 69.5 (t,  $\text{CH}_2\text{O}$ ), 112.1, 114.0 (2 d, C-3<sub>Furyl</sub>, C-4<sub>Furyl</sub>), 118.0, 128.9, 131.9, 144.1, 150.0, 151.3 (3 d, 3 s, C-2', C-3', C-2, C-3, C-2<sub>Furyl</sub>, C-5<sub>Furyl</sub>), 168.2 (s, C-1'), 201.2 (s, C-3) ppm; IR (neat):  $\tilde{\nu}$  = 3220 (NH), 2955–2870 (=CH, C-H), 1702–1620

(C=O, C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$  calcd. for  $\text{C}_{20}\text{H}_{31}\text{NO}_4\text{NaSi}$ : 400.1920, found 400.1927.

**(E)-N-((E)-3-Oxo-1-phenyl-2-[2-(trimethylsilyl)ethoxy]but-1-enyl)but-2-enamide (1j):** According to typical procedure 1, a mixture of TMSE-allene **4** (2.12 mL, 14.5 mmol), *n*-butyllithium (5.81 mL, 14.5 mmol, 2.5 M in hexanes), benzonitrile (0.50 g, 4.85 mmol) and crotonic acid (1.99 mL, 23.1 mmol) in dry diethyl ether (40 mL) gave 0.845 g (46 %) of  $\beta$ -ketoenamide **1j** as a pale yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –0.17 (s, 9 H,  $\text{SiMe}_3$ ), 0.62–0.66 (m, 2 H,  $\text{SiCH}_2$ ), 1.85 (dd,  $J$  = 6.8, 1.7 Hz, 3 H, Me), 2.34 (s, 3 H, Me), 3.26–3.31 (m, 2 H,  $\text{OCH}_2$ ), 5.92 (dd,  $J$  = 15.2, 1.4 Hz, 1 H, =CH), 6.79–6.88 (m, 1 H, =CH), 7.25–7.42 (m, 5 H, Ph), 11.45 (s, 1 H, NH) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –1.6 (q,  $\text{SiMe}_3$ ), 18.0 (q, C-4'), 18.7 (t,  $\text{CH}_2\text{Si}$ ), 27.5 (q, Me), 71.4 (t,  $\text{CH}_2\text{O}$ ), 125.9, 127.7, 128.4, 128.7, 132.7, 137.3, 142.7, 143.1 (5 d, 3 s, C-2', C-3', C-1, C-2, Ph), 164.2 (s, C-1'), 202.5 (s, C-3) ppm; IR (neat):  $\tilde{\nu}$  = 3305 (NH), 3015–2955 (=C-H, C-H), 1700–1565 (C=O, C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$  calcd. for  $\text{C}_{19}\text{H}_{27}\text{NO}_3\text{NaSi}$ : 368.1658, found 368.1650.

**N-((E)-3-Oxo-1-phenyl-2-[2-(trimethylsilyl)ethoxy]but-1-enyl)cinnamamide (1k):** According to typical procedure 1, a mixture of TMSE-allene **4** (2.12 mL, 14.5 mol), *n*-butyllithium (5.81 mL, 14.5 mmol, 2.5 M in hexanes), benzonitrile (0.50 g, 4.85 mmol) and cinnamic acid (4.31 g, 29.1 mmol) in dry diethyl ether (40 mL) gave 1.00 g (50 %) of  $\beta$ -ketoenamide **1k** as a pale yellow solid. M. p. 68–72 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –0.14 (s, 9 H,  $\text{SiMe}_3$ ), 0.66–0.70 (m, 2 H,  $\text{SiCH}_2$ ), 2.38 (s, 3 H, Me), 3.32–3.36 (m, 2 H,  $\text{OCH}_2$ ), 5.54 (d,  $J$  = 15.6 Hz, 1 H, =CH), 7.34–7.42, 7.46–7.51 (2 m, 6 H, 4 H, Ph), 7.71 (d,  $J$  = 15.6 Hz, 1 H, =CH), 11.72 (s, 1 H, NH) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –1.5 (q,  $\text{SiMe}_3$ ), 18.7 (t,  $\text{CH}_2\text{Si}$ ), 27.6 (q, Me), 71.5 (t,  $\text{CH}_2\text{O}$ ), 121.0, 127.8, 128.2, 128.5, 128.7, 128.9, 130.2, 132.7, 134.5, 137.4, 143.1, 143.4 (6 d, 4 s, 2 d, C-2', C-3', C-1, C-2, Ph), 164.3 (s, C-1'), 202.6 (s, C-3) ppm; IR (KBr):  $\tilde{\nu}$  = 3275 (NH), 3065–2895 (=C-H, C-H), 1695–1630 (C=O, C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$  calcd. for  $\text{C}_{24}\text{H}_{29}\text{NO}_3\text{NaSi}$ : 430.1809, found 430.1825;  $\text{C}_{24}\text{H}_{29}\text{NO}_3\text{Si}$  (407.6): calcd. C, 70.72, H, 7.17, N, 3.44; found C, 70.07, H, 6.10, N, 3.20.

**(E)-N-((E)-3-Oxo-1-phenyl-2-[2-(trimethylsilyl)ethoxy]but-1-enyl)acetamide (1l):** According to typical procedure 1, a mixture of TMSE-allene **4** (0.58 mL, 4.00 mmol), *n*-butyllithium (1.4 mL, 3.50 mmol, 2.5 M in hexanes), benzonitrile (0.50 g, 4.85 mmol) and acetic acid (0.75 mL, 9.60 mmol) in dry diethyl ether (20 mL) gave 0.255 g (23 %) of  $\beta$ -ketoenamide **1l** as a pale yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –0.17 (s, 9 H,  $\text{SiMe}_3$ ), 0.62–0.67 (m, 2 H,  $\text{SiCH}_2$ ), 2.07, 2.34 (2 s, 3 H each, Me), 3.25–3.30 (m, 2 H,  $\text{OCH}_2$ ), 7.35–7.40 (m, 5 H, Ph), 11.2 (s, 1 H, NH) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –1.6 (q,  $\text{SiMe}_3$ ), 18.7 (t,  $\text{CH}_2\text{Si}$ ), 25.0, 27.6 (2 q, Me), 71.4 (t,  $\text{CH}_2\text{O}$ ), 127.8, 128.6, 128.8, 132.7, 137.4, 142.3 (3 d, 3 s, C-2', C-3', Ph), 169.0 (s, C-1'), 202.5 (s, C-3) ppm; IR (neat):  $\tilde{\nu}$  = 3270 (NH), 3060–2890 (=C-H, C-H), 1685–1630 (C=O, C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$  calcd. for  $\text{C}_{17}\text{H}_{25}\text{NO}_3\text{NaSi}$ : 342.1496, found 342.1486.

**N-(2,2-Dimethyl-4,5-dioxohexan-3-yl)acrylamide (3e), Typical Procedure 2:**  $\beta$ -Ketoenamide **1e** (160 mg, 0.514 mmol) and trifluoroacetic acid (5 mL) were heated to 80 °C in a sealed tube for 15 min. After cooling to room temperature, water was slowly added and the resulting mixture was extracted 2–3 times with dichloromethane. The combined organic layers were dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Purification by column chromatography ( $\text{SiO}_2$ , hexanes/ $\text{EtOAc}$  40 %) provided 79 mg (73 %) of 1,2-diketone **3e** as pale yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.94 (s, 9 H, *t*Bu), 2.32 (s, 3 H, Me), 5.25 (d,  $J$  = 7.6 Hz, 1 H, CH), 5.64 (dd,  $J$  = 9.2, 1.6 Hz, 1 H, =CH<sub>2</sub>), 6.10–6.27 (m, 3 H, =CH<sub>2</sub>, NH) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 23.4 (q, Me), 26.7, 35.0 (q, s, *t*Bu), 58.1 (d, C-1), 127.6, 129.8 (d, t, C-2', C-3'), 165.5 (s, C-1'), 196.3, 198.1 (2 s,



C-2, C-3) ppm; IR (neat):  $\tilde{\nu}$  = 3300 (NH), 2960–2855 (=C–H, C–H), 1710–1660 (C=O), 1620–1530 (C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd. for C<sub>11</sub>H<sub>17</sub>NO<sub>3</sub>Na: 234.1101, found 234.1105.

**(E)-N-(2,2-Dimethyl-4,5-dioxohexan-3-yl)but-2-enamide (3f):** According to typical procedure 2,  $\beta$ -ketoenamide enamide **1f** (225 mg, 0.69 mmol) in trifluoroacetic acid (5 mL) gave 124 mg (80 %) of 1,2-diketone **3f** as pale yellow solid. M. p. 73–76 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.93 (s, 9 H, tBu), 1.79–1.81 (m, 3 H, Me), 2.31 (s, 3 H, Me), 5.17 (d,  $J$  = 7.4 Hz, 1 H, CH), 5.81–5.83 (dd,  $J$  = 15.2, 1.1 Hz, 1 H, =CH), 6.11–6.18 (m, 1 H, NH), 6.74–6.83 (m, 1 H, =CH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 17.8 (q, C-4), 23.5 (q, Me), 26.7, 34.8 (q, s, tBu), 58.1 (d, C-1), 124.0, 141.3 (2 d, C-2', C-3'), 165.9 (s, C-1'), 196.4, 198.1 (2 s, C-2, C-3) ppm; IR (KBr):  $\tilde{\nu}$  = 3285 (NH), 2960–2865 (=CH, C–H), 1720–1670 (C=O), 1605–1520 (C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd. for C<sub>12</sub>H<sub>19</sub>NO<sub>3</sub>Na: 248.1263, found 248.1224; C<sub>12</sub>H<sub>19</sub>NO<sub>5</sub> (225.1): calcd. C, 63.98; H, 6.50; N, 6.22; found C, 64.48; H, 6.66; N, 5.76.

**N-(2,2-Dimethyl-4,5-dioxohexan-3-yl)cinnamamide (3g):** According to typical procedure 2,  $\beta$ -ketoenamide **1g** (300 mg, 0.775 mmol) in trifluoroacetic acid (5 mL) gave 133 mg (60 %) of 1,2-diketone **3g** as pale yellow solid. M. p. 75–78 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.99 (s, 9 H, tBu), 2.36 (s, 3 H, Me), 5.34 (d,  $J$  = 7.4 Hz, 1 H, CH), 6.34 (d<sub>br</sub>,  $J$  = 4.9 Hz, 1 H, NH), 6.47 (dd,  $J$  = 15.6, 1.0 Hz, 1 H, =CH), 7.33–7.35, 7.46–7.49 (2 m, 3 H, 2 H, Ph), 7.60 (d,  $J$  = 15.6 Hz, 1 H, =CH) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 23.5 (q, Me), 26.8, 35.1 (q, s, tBu), 58.3 (d, C-1), 119.3, 128.0, 128.9, 130.0, 134.5, 142.5 (5 d, s, C-2', C-3', Ph), 166.2 (s, C-1'), 196.4, 198.1 (2 s, C-2, C-3) ppm; IR (KBr):  $\tilde{\nu}$  = 3305 (NH), 2955–2875 (=C–H, C–H), 1705–1685 (C=O), 1630 (C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd. for C<sub>17</sub>H<sub>21</sub>NO<sub>3</sub>Na: 310.1414, found 310.1422.

**(E)-N-(2,2-Dimethyl-4,5-dioxohexan-3-yl)-3-(4-nitrophenyl)acrylamide (3h):** According to typical procedure 2, enamide **1h** (200 mg, 0.69 mmol) in trifluoroacetic acid (4 mL) gave 84 mg (55 %) of 1,2-diketone **3h** as pale yellow solid. M. p. 132–134 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.99 (s, 9 H, tBu), 2.36 (s, 3 H, Me), 5.35 (d,  $J$  = 7.6 Hz, 1 H, CH), 6.28 (d<sub>br</sub>,  $J$  = 7.6 Hz, 1 H, NH), 6.37 (d,  $J$  = 15.5 Hz, 1 H, =CH), 7.49–7.62 (m, 3 H, Ar), 7.97–8.01 (m, 2 H, =CH, Ar) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 23.5 (q, Me), 26.8, 35.1 (q, s, tBu), 58.3 (d, C-1), 124.8, 124.9, 129.2, 130.0, 130.9, 133.4, 137.4, 148.3 (6 d, 2 s, C-2', C-3', Ar), 164.8 (s, C-1'), 196.3, 198.1 (2 s, C-2, C-3) ppm; IR (KBr):  $\tilde{\nu}$  = 3295 (NH), 2965–2875 (=C–H, C–H), 1710–1655 (C=O), 1615–1580 (C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd. for C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>Na: 355.1270, found 355.1268.

**(E)-N-(2,2-Dimethyl-4,5-dioxohexan-3-yl)-3-(furan-2-yl)acrylamide (3i):** According to typical procedure 2, enamide **1i** (50 mg, 0.13 mmol), in trifluoroacetic acid (3 mL) gave 25 mg (70 %) of 1,2-diketone **3i** as pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.97 (s, 9 H, tBu), 2.35 (s, 3 H, MeCO), 5.33 (d,  $J$  = 7.4 Hz, 1 H, CH), 6.35 (d,  $J$  = 15.3 Hz, 1 H, =CH), 6.41–6.43 (m, 1 H, Furyl), 6.54 (d,  $J$  = 3.3 Hz, 1 H, Furyl), 7.35 (d,  $J$  = 15.3 Hz, 1 H, =CH), 7.41 (d,  $J$  = 3.1 Hz, 1 H, Furyl); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 23.5 (q, Me), 26.7, 35.1 (q, s, tBu), 58.3 (d, C-1), 112.3, 114.6 (2 d, C-3<sub>Furyl</sub>, C-4<sub>Furyl</sub>), 116.9, 128.9, 144.4, 151.0 (3 d, s, C-2', C-3', C-2<sub>Furyl</sub>, C-5<sub>Furyl</sub>), 166.2 (s, C-1'), 196.3, 198.0 (2 s, C-2, C-3) ppm; IR (neat):  $\tilde{\nu}$  = 3250 (NH), 2965–2880 (=CH, C–H), 1710–1660 (C=O), 1620–1530 (C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd. for C<sub>15</sub>H<sub>19</sub>NO<sub>4</sub>Na: 300.1212, found 300.1233.

**(E)-N-(2,3-Dioxo-1-phenylbutyl)but-2-enamide (3j) and Compound 5j:** According to typical procedure 2, enamide **1j** (430 mg, 1.25 mmol) in trifluoroacetic acid (5 mL) gave 91 mg (30 %) of 1,2-diketone **3j** as pale yellow oil and 84 mg (30 %) of compound **5j** as pale yellow solid. Data for **3j**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.82–

1.84 (m, 3 H, =CHMe), 2.28 (s, 3 H, COMe), 5.83–5.87 (m, 1 H, =CHCO), 6.21 (d,  $J$  = 5.6 Hz, 1 H, CH), 6.46 (s<sub>br</sub>, 1 H, NH), 6.79–6.88 (m, 1 H, =CHMe), 7.29–7.34 (m, 5 H, Ph) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 17.8 (q, Me), 24.3 (q, 3'-Me), 57.5 (d, C-1), 123.8, 128.5, 128.9, 129.3, 134.0, 141.7 (5 d, s, C-2', C-3', Ph), 165.5 (s, C-1'), 192.8, 196.1 (2 s, C-2, C-3) ppm; IR (neat):  $\tilde{\nu}$  = 3305 (NH), 3020–2835 (=C–H, C–H), 1700, 1675 (C=O), 1640–1505 (C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd. for C<sub>14</sub>H<sub>15</sub>NO<sub>3</sub>Na: 268.0950, found 268.0986. Data for dimer **5j**: M. p. > 220 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.41 (s, 6 H, Me), 1.88 (d,  $J$  = 6.8 Hz, 6 H, Me), 6.00 (d,  $J$  = 15.2 Hz, 2 H, =CH), 6.87–6.96 (m, 2 H, =CH), 7.27–7.37 (m, 6 H, Ar), 7.69 (d,  $J$  = 7.2 Hz, 2 H, Ar), 8.19 (s<sub>br</sub>, 2 H, NH) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.5 (q, Me), 17.9 (q, Me), 57.1 (s, C-1), 72.2 (s, C-3), 122.3, 124.4, 124.7, 129.2, 129.6, 137.9, 139.0, 142.1 (6 d, 2 s, C-2', C-3', Ar), 167.2 (s, C-1'), 199.2 (s, C-2) ppm; IR (KBr):  $\tilde{\nu}$  = 3355 (NH), 3020–2875 (=C–H, C–H), 1775, 1680 (C=O), 1640–1505 (C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd. for C<sub>28</sub>H<sub>27</sub>N<sub>2</sub>O<sub>4</sub>Na: 477.1868, found 477.1829.

**N-(2,3-Dioxo-1-phenylbutyl)cinnamamide (3k) and Compound 5k:** According to typical procedure 2, enamide **1k** (80 mg, 0.196 mmol) in trifluoroacetic acid (2 mL) gave 19 mg (33 %) of 1,2-diketone **3k** and 14 mg (25 %) of compound **5k** as pale yellow oils. Data for **3k**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.31 (s, 3 H, Me), 6.33 (d,  $J$  = 5.8 Hz, 1 H, CH), 6.46 (d,  $J$  = 15.6 Hz, 1 H, =CH), 6.63 (s<sub>br</sub>, 1 H, NH), 7.25–7.49 (m, 10 H, Ph), 7.62 (d,  $J$  = 15.6 Hz, 1 H, =CH) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 24.4 (q, Me), 57.7 (d, C-1), 128.0, 128.4, 128.9, 129.0, 129.4, 130.0, 130.7, 133.9, 134.5, 142.5 (8 d, 2 s, C-2', C-3', Ph), 165.5 (s, C-1'), 192.8, 196.0 (2 s, C-2, C-3) ppm; IR (neat):  $\tilde{\nu}$  = 3405 (NH), 3020 (=C–H, C–H), 1705, 1675 (C=O), 1620 (C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd. for C<sub>19</sub>H<sub>17</sub>NO<sub>3</sub>Na: 330.1106, found 330.1156. Data for compound **5k**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.46 (s, 6 H, Me), 6.62 (d,  $J$  = 15.5 Hz, 2 H, =CH), 7.31–7.37, 7.54–7.56 (2 m, 14 H, 4 H, Ar, Ph), 7.72 (d,  $J$  = 15.6 Hz, 2 H, =CH), 8.44 (s<sub>br</sub>, 2 H, NH) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.6 (q, Me), 57.2 (s, C-1), 72.5 (s, C3), 120.1, 122.4, 124.5, 128.2, 128.9, 129.4, 129.7, 130.1, 134.5, 137.9, 139.1, 142.9 (9 d, 3 s, C-2', C-3', Ar, Ph), 167.3 (s, C-1'), 199.8 (s, C-2) ppm; IR (KBr):  $\tilde{\nu}$  = 3340 (NH), 3070–2980 (=C–H, C–H), 1780, 1665 (C=O), 1625–1510 (C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + H]<sup>+</sup> calcd. for C<sub>38</sub>H<sub>31</sub>N<sub>2</sub>O<sub>4</sub>: 579.2278, found 579.2296.

**Oxazole 2l and Compound 5l:** According to typical procedure 2, enamide **1l** (75 mg, 0.219 mmol) in trifluoroacetic acid (2 mL) gave 6.5 mg (15 %) of oxazole **2l** as a colorless solid and 5 mg (12 %) of compound **5l** as a pale yellow oil. Data for oxazole **2l**:<sup>[21]</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.51, 2.65 (2 s, 3 H each, Me), 7.44–7.48, 8.13–8.15 (2 m, 3 H, 2 H, Ph) ppm. HRMS:  $m/z$  [M + H]<sup>+</sup> calcd. for C<sub>16</sub>H<sub>12</sub>NO<sub>2</sub>: 202.0863, found 202.0866. Data for compound **5l**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.41, 2.14 (2 s, 6 H each, Me), 7.27–7.38, 7.67–7.69 (2 m, 6 H, 2 H, Ar), 8.05 (s<sub>br</sub>, 2 H, NH) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.5, 23.8 (2 q, Me), 57.1 (s, C-1), 72.1 (s, C-3), 122.5, 124.4, 129.3, 129.7, 137.8, 139.1 (4 d, 2 s, Ar), 171.9 (s, C-1'), 199.9 (s, C-2) ppm; IR (neat):  $\tilde{\nu}$  = 3340 (NH), 3070–2980 (=C–H, C–H), 1780, 1665 (C=O)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd. for C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>Na: 425.1472, found 425.1463.

**N-[2,2-Dimethyl-1-(3-methylquinoxalin-2-yl)propyl]acrylamide (6e), Typical Procedure 3:** 1,2-diketone **3e** (66 mg, 0.31 mmol), *o*-phenylenediamine (41 mg, 0.37 mmol), cerium(IV) ammonium nitrate (17 mg, 0.03 mmol) and water (2.5 mL) were stirred for 1 h at room temperature. The mixture was quenched with ethyl acetate (2 mL) and washed three times with water. The organic phase was dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated to dryness. The product was purified by column chromatography (SiO<sub>2</sub>, hexanes/EtOAc 10 %) furnishing **6e** (45 mg, 51 %) as a colorless solid. M. p. 131–134 °C;

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.00 (s, 9 H, tBu), 2.90 (s, 3 H, Me), 5.58–5.64 (m, 2 H, CH, =CH), 6.16–6.31 (m, 2 H, =CH<sub>2</sub>), 6.88 (d<sub>br</sub>,  $J$  = 9.4 Hz, 1 H, NH), 7.62–7.69 (m, 2 H, Quin-H), 7.95–7.98 (m, 2 H, Quin-H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 23.5 (q, Me), 26.6, 37.8 (q, s, tBu), 56.0 (d, C-1), 126.8, 128.5, 128.7, 129.0, 129.7, 130.9, 140.4, 141.1, 153.0, 154.8 (t, 5 d, 4 s, C-2', C-3', Quin-C), 165.1 (s, C-1') ppm; IR (KBr):  $\tilde{\nu}$  = 3290 (NH), 3070–2965 (=C–H, C–H), 1660–1650 (C=O, C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd. for C<sub>17</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub>: 306.1582, found 306.1576.

**(E)-N-[2,2-Dimethyl-1-(3-methylquinoxalin-2-yl)propyl]but-2-enamide (6f)**: According to typical procedure 3, a mixture of 1,2-diketone **3f** (65 mg, 0.28 mmol), *o*-phenylenediamine (38 mg, 0.35 mmol) and cerium (IV) ammonium nitrate (16 mg, 0.29 mmol) in water (3 mL) gave quinoxaline **6f** (50 mg, 58 %) as colorless solid. M. p. 154–156 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.00 (s, 9 H, tBu), 1.81–1.83 (dd,  $J$  = 6.8, 1.7 Hz, 3 H, Me), 2.90 (s, 3 H, Me), 5.58 (d,  $J$  = 9.5 Hz, 1 H, CH), 5.88–5.92 (dd,  $J$  = 15.2, 1.7 Hz, 1 H, =CH), 6.69 (d<sub>br</sub>,  $J$  = 9.4 Hz, 1 H, NH), 6.79–6.88 (m, 1 H, =CH), 7.64–7.69 (m, 2 H, Quin-H), 7.96 (m, 2 H, Quin-H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 17.7 (q, Me), 23.6 (q, Me), 26.6, 37.7 (q, s, tBu), 55.8 (d, C-1), 125.1, 128.5, 128.7, 129.0, 129.7, 140.3, 140.4, 141.1, 153.0, 155.1 (6 d, 4 s, C-2', C-3', Quin-H), 165.1 (s, C-1') ppm; IR (KBr):  $\tilde{\nu}$  = 3285 (NH), 3060–2920 (=CH, C-H), 1665–1535 (C=O, C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd. for C<sub>18</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>: 320.1739, found 320.1745.

**N-[2,2-Dimethyl-1-(3-methylquinoxalin-2-yl)propyl]cinnamamide (6g)**: According to typical procedure 3, a mixture of 1,2-diketone **3g** (75 mg, 0.26 mmol), *o*-phenylenediamine (33 mg, 0.31 mmol) and cerium(IV) ammonium nitrate (14 mg, 0.025 mmol) in water (2.5 mL) gave quinoxaline **6g** (50 mg, 53 %) as a colorless solid. M. p. 176–178 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.05 (s, 9 H, tBu), 2.94 (s, 3 H, Me), 5.67 (d,  $J$  = 9.4 Hz, 1 H, CH), 6.73 (d,  $J$  = 15.6 Hz, 1 H, =CH), 6.94 (d,  $J$  = 9.4 Hz, 1 H, NH), 7.31–7.33, 7.47–7.49 (2 m, 3 H, 2 H, Ph), 7.63 (d,  $J$  = 15.6 Hz, 1 H, =CH), 7.67–7.70 (m, 2 H, Quin-H), 7.98–8.02 (m, 2 H, Quin-H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 23.6 (q, Me), 26.7, 37.8 (q, s, tBu), 56.1 (d, C-1), 120.7, 127.9, 128.5, 128.8, 129.1, 129.7, 134.8, 140.4, 141.1, 141.5, 153.1, 155.0 (8 d, 4 s, C-2', C-3', Ph, Quin-C), 165.5 (s, C-1') ppm; IR (KBr):  $\tilde{\nu}$  = 3295 (NH), 3060–2870 (=C–H, C–H), 1660–1615 (C=O, C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + Na]<sup>+</sup> calcd. for C<sub>23</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>: 382.1895, found 382.1888.

**(E)-3-(Furan-2-yl)-N-[(3-methylquinoxalin-2-yl)(phenyl)methyl]acrylamide (6i)**: According to typical procedure 3, a mixture of 1,2-diketone **3i** (68 mg, 0.24 mmol), *o*-phenylenediamine (31.8 mg, 0.28 mmol) and cerium (IV) ammonium nitrate (13 mg, 0.024 mmol) in water (2.5 mL) afforded quinoxaline **6i** (47 mg, 55 %) as a brownish oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.03 (s, 9 H, tBu), 2.92 (s, 3 H, Me), 5.64 (d,  $J$  = 9.5 Hz, 1 H, CH), 6.39–6.43 (m, 2 H, =CH, Furyl-H), 6.50 (d,  $J$  = 3.2 Hz, 1 H, Furyl-H), 6.89 (d,  $J$  = 9.5 Hz, 1 H, NH), 7.38 (d,  $J$  = 15.2 Hz, 2 H, Furyl-H, =CH), 7.64–7.70 (m, 2 H, Quin-H), 7.96–8.01 (m, 2 H, Quin-H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 23.6 (q, Me), 26.7, 37.8 (q, s, tBu), 56.1 (d, C-1), 112.2, 113.8, 118.5, 128.2, 128.5, 128.7, 128.0, 129.7, 140.0, 141.1, 144.0, 151.3, 153.3, 155.0 (9 d, 5 s, C-2', C-3', Furyl-C, Quin-H), 165.4 (s, C-1') ppm; IR (neat):  $\tilde{\nu}$  = 3295 (NH), 3050–2875 (=CH, C-H), 1670–1610 (C=O, C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + H]<sup>+</sup> calcd. for C<sub>21</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub>: 350.1869, found 350.1874.

**N-[(3-Methylquinoxalin-2-yl)(phenyl)methyl]cinnamamide (6k)**: According to typical procedure 3, a mixture of 1,2-diketone **3k** (20 mg, 0.065 mmol), *o*-phenylenediamine (8.4 mg, 0.078 mmol) and cerium(IV) ammonium nitrate (3.5 mg, 0.006 mmol) in water (2.5 mL) afforded quinoxaline **6k** (10 mg, 42 %) as a colorless oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.65 (s, 3 H, Me), 6.46 (d,  $J$  = 7.3 Hz,

1 H, CH), 6.59 (d,  $J$  = 15.6 Hz, 1 H, =CH), 6.63 (d,  $J$  = 7.3 Hz, 1 H, NH), 7.24–7.40 (m, 10 H, Ph), 7.51–7.54 (m, 2 H, Quin-H), 7.66 (d,  $J$  = 15.6 Hz, 1 H, =CH), 7.75–7.79 (m, 2 H, Quin-H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 22.4 (q, Me), 54.7 (d, C-1), 117.1, 120.7, 127.9, 128.2, 128.5, 128.8, 128.9, 129.4, 129.7, 129.9 (8 d, 2 s, C-2', C-3', Ph), 130.7, 134.9, 139.2, 139.9, 141.5, 141.7, 152.6, 152.7 (4 d, 4 s, Quin-C), 164.8 (s, C-1') ppm; IR (neat):  $\tilde{\nu}$  = 3300 (NH), 3065–2855 (=C–H, C–H), 1680–1620 (C=O, C=C)  $\text{cm}^{-1}$ ; HRMS:  $m/z$  [M + H]<sup>+</sup> calcd. for C<sub>25</sub>H<sub>22</sub>N<sub>3</sub>O: 380.1763, found 380.1756.

### Crystal Structure Determination

X-ray single crystal diffraction of compound **5j** was performed on a Bruker AXS Smart CCD. The structures were solved by direct methods, using SHELXS-97.<sup>[22]</sup> Refinement was done with the least-squares method (SHELXL Version 2017/1).<sup>[22]</sup> Molecular Graphics: ORTEP-3 for Windows.

CCDC 1973331 (for **5j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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